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Research Article

Study of the Putative Influence of beta3 Adrenoceptor Agonism on Brain Oxygen Tension and Blood Flow; a Flow Oxymetry Study in the Rat Medial-Prefrontal Cortex

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Abstract

It has been reported that stimulation of the beta3 receptor resulted in strong anxiolytic- like outcome as well as antidepressant-like effects in acute or chronic models of depression in rodents. In addition this appears devoid of side effects related to cognition, motor activity, alcohol interaction or physical dependence. In previous work the methodology of in vivo flow oxymetry has been applied to analyze the influence of another class of receptor agonist upon tissue oxygen tension (pO2), and blood flow (cBF) in the rat brain. In the present study flow oxymetry has been applied in the medial-prefrontal cortex of anaesthetised rats so that to study the putative influence of the beta3 adrenoceptor agonist SB2039X on oxygen tension and blood flow.

Keywords: rat brain; medial-prefrontal cortex; beta3 receptor; flow oxymetry

Introduction

It has been reported that stimulation of the beta3 receptor resulted in strong anxiolytic- like outcome, similar to those attained with the benzodiazepine diazepam or chlordiazepoxide. Furthermore, treatment with beta3 adrenoceptor agonist resulted in antidepressant-like effects in acute or chronic models of depression in rodents, such as the forced-swimming and the chronic mild stress tests. Effects that is comparable in terms of the magnitude to those of the antidepressant fluoxetine or imipramine. In addition the first selective orally active and brain-penetrant beta3 adrenoceptor agonist, SR58611A (amibegron) was devoid of side effects related to cognition (as shown in the Morris water maze and object recognition tasks), motor activity (in the rotarod), alcohol interaction, or physical dependence (Stemmelin et al. 2008). In previous work the methodology of in vivo flow oxymetry has been applied to analyze the influence of another class of receptor agonist upon tissue oxygen tension (pO2), and blood flow (cBF) in the rat brain. For instance the results gathered corroborate an influence of the PPAR gamma receptor agonist studied on the metabolic activity recorded in the medial prefrontal cortex (mpfcx). This is further supporting the flow-oxymetry methodology as valuable tool for in vivo investigation in brain discrete areas (Crespi 2020a,b). In the present study flow oxymetry has been applied in the medial-prefrontal cortex of anaesthetised rats so that to study the putative influence of the beta3 adrenoceptor agonist SB2039X on oxygen tension and blood flow.

Methods

In vivo oxymetry

The oxylite/LDF/T probe (approx. 0.3 mm diameter) was lowered stereotactically in the medial-prefrontal cortex (mpfcx) of anaesthetized (1 % isoflurane in a 30 %/70 % O2:N2 mixture) adult male rats according to the coordinates from Paxinos and Watson (1986) i.e. AP +3.0 mm, ML +0.5 mm and DV −4.5 mm. Prior to that, each rat was tracheotomized and artificially ventilated with a mechanical respirator (Inspira, Oxford, UK). The right femoral artery was cannulated with a PE50 polyethylene catheter for: [1]. monitoring arterial blood pressure, [2]. “blood gas analysis” and [3]. infusion of compounds, that is, d-tubocurarine (0.25 mg/kg/h, dissolved in saline heparin (25 UI/ml)) to maintain muscle relaxation. Throughout surgery, the “gas” anaesthetic level was maintained at 2.5 % isoflurane, while during measurements this level was lowered to 1 %. Further details of the protocol used here are described in Ceolin (2007). Fluorescence quenching spectroscopy and laser Doppler

flowmetry are then performed in parallel for the simultaneous measurement of brain tissue oxygen tension (pO2) and cerebral blood flow (cBF) (Crespi 2013).

Treatments

The pO2–cBF real-time measurements were started as soon as the probe was lowered into the mpfcx (n = 4) following coordinates described above. Following a period of stabilization of the physiological signals recorded (approximately 1, 1.5 h), rats were challenged with:

1. O2 during 2 min (i.e., the mixture 30 %/70 % O2:N2 was changed to 100 % O2 by stopping N2 supply).

2. 5 % CO2 during 1 min (i.e., 0.1 l/min CO2 were added to the O2:N2 mixture).

3. SB2039X 10mg/kg i.p. dissolved in water (vehicle) n=6. The dose was selected based on the literature (i.e. effective dose increasing significantly punished responses in the punished drinking test (Vogel test) in rats; (Stemmelin et al. 2008).

4. Vehicle (water, 2.5ml/kg i.p.) n=4.

Results

Treatments 1 and 2 were performed to verify the correct response of the probe to an increased level of cerebral O2 (via addition of exogenous O2, 3min) up to approximately 250% of control values as well as to CO2 - induced mild hypercapnia (CO2 5%, 1.5min) up to approximately 340% of control values. It appeared that both O2 and CO2 challenges were increasing transiently (few minutes) pO2 values, with a different effect on blood flow that was unaltered by O2 challenge while it was transiently increased following CO2 challenge up to approximately 150% of control values (figure 1).

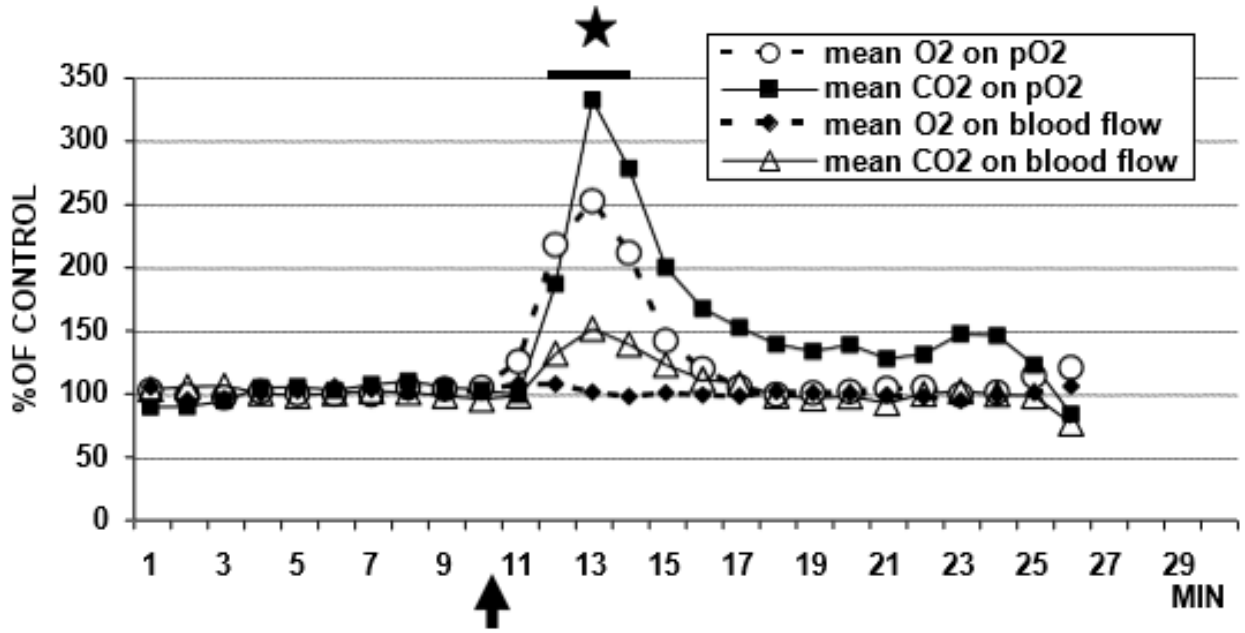

Figure 1: pO2 and blood flow values were sampled every 1 min before and after O2 or CO2 challenge (arrow). Data are in % of basal pre-treatment levels, n = 4. S.D. are not shown for clarity. Both O2 and CO2 challenges were increasing transiently (few minutes) but significantly pO2 values. Similarly blood flow was significantly, although transiently, increased by CO2 challenge while no significant differences were observed on pO2 levels. $p < 0.05$, Fisher's LSD test.

These data are very similar to those reported earlier (Crespi) Treatments 3 and 4 were performed to verify the putative influence of the beta3 adrenoceptor agonist SB2039X on oxygen tension and blood flow. It appeared that no significant variations of the two parameters monitored (pO2 and cBF) were monitored when treating anaesthetised rats with such compound versus vehicle (see figure 2).

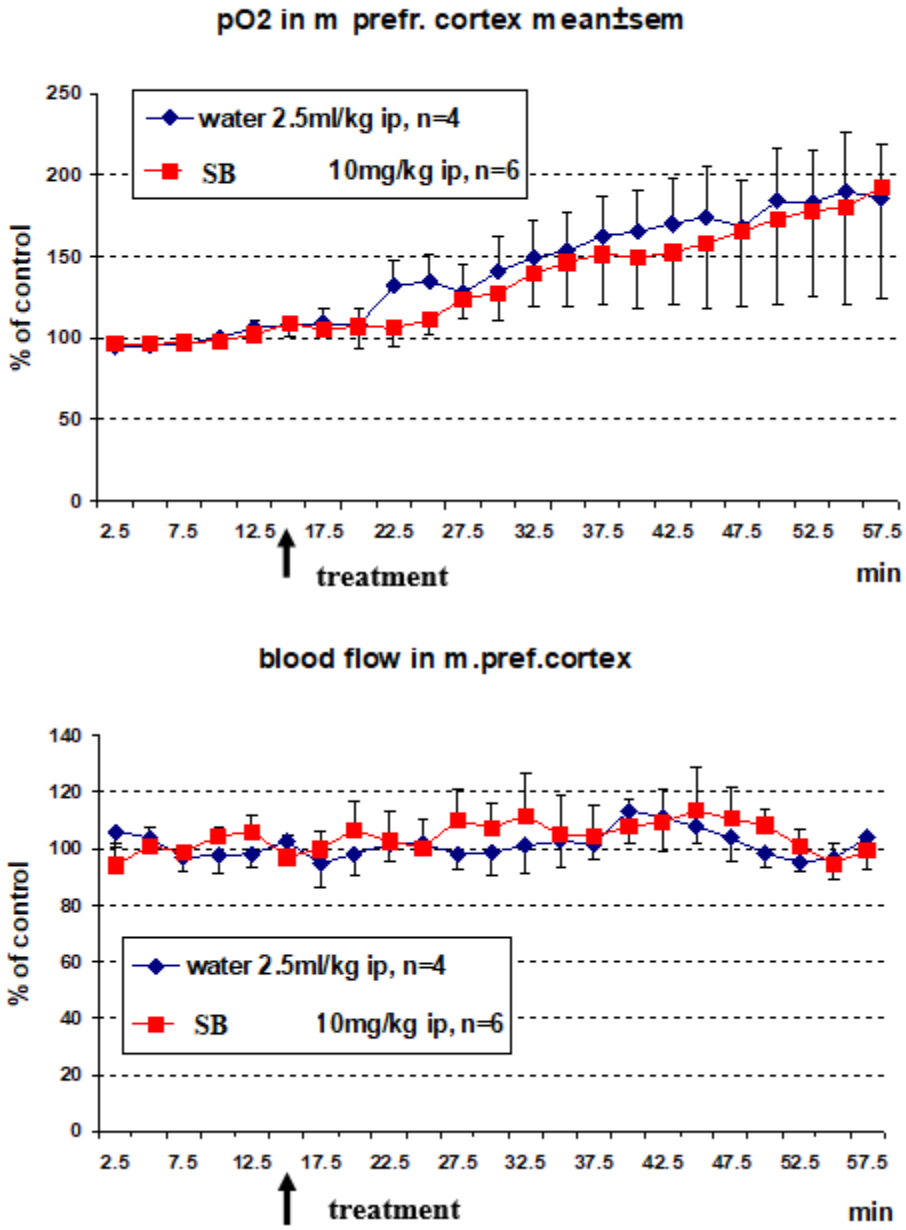

Figure 2: Effect of the beta3 adrenoceptor agonist SB2039X (n=6) or vehicle (water n=4) on oxygen tension (pO2) and blood flow recorded in the medial prefrontal cortex of anaesthetised rats. Data are in % of basal pre-treatment levels,mean ± SD. No significant changes are observed for both parameters

Discussion

This study has been performed by means of a combined Oxylite/LDF system (Oxford Optronix, Oxford, UK) to simultaneously measure tissue oxygen tension (pO2), and blood flow (cBF) in the rat brain via a combined dual fluorescence-quenching/Laser Doppler- Flowmetry probe described previously (Crespi 2013). The present data indicate the methodology as able to distinguish changes in pO2 – cBF parameters induced either via application of exogenous oxygen or via CO2 - induced mild hypercapnia. Therefore they further support the methodology as useful tool to monitor oxygen tension (pO2) and blood flow in discrete brain areas such as medial prefrontal cortex as well as in striatum (Crespi 2013, 2020). Changes in tissue pO2 reflect transient imbalance between oxygen consumption and supply, and are sensitive to local changes in oxygen metabolic rate (Rhodes et al. 2022). Therefore, this methodology is applied to analyse the concept of the "metabolic hypothesis of depression" as evoked by former works (Bremner et al. 2003; Moylan et al. 2013; Pizzagalli 2014; Pizzagalli and Roberts 2022). Previous work proposed that stimulation of the β3 receptor resulted in strong anxiolytic-like ending and in antidepressant-like effects in acute or chronic models of depression in rodents. Moreover the first selective orally active and brain-penetrant beta3 adrenoceptor agonist amibegron was devoid of side

effects related to cognition, motor activity, alcohol interaction, or physical dependence (Stemmelin et al., 2008; Tamburella et al.2010; Schena and Caplan 2019). In the present work the putative influence of the beta3 adrenoceptor agonist SB2039X on oxygen tension and blood flow in discrete brain regions was examined. Indeed, the feasibility of such estimation has been demonstrated in a recent study where the in vivo investigation of pharmacological effects of psychostimulants and anticonvulsants (Crespi 2020a) as well as other receptor agonist (Crespi 2020b) on cerebral oxygen metabolism in selected brain regions has been achieved. In addition, the data obtained here with the beta3 adrenoceptor SB2039X indicate that there is no significant modification of oxygen Tension pO2 and Blood Flow in the Medial-Prefrontal Cortex, thus indicating lack of influence on local medial prefrontal cortex metabolic activity of the beta3 adrenoceptor agonist. This may correlate to the reported lack of side effects of such chemicals therefore further supporting the pharmacological stimulation of the beta3 adrenoceptor as a novel, less detrimental treatment strategy for anxiety and depressive disorders.

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References

1. Stemmelin, J., Cohen, C., Terranova, J. P., Lopez-Grancha, M., Pichat, P., et.al. (2008) . Stimulation of the beta3 adrenoceptor as a novel treatment strategy for anxiety and depressive disorders. *Neuropsychopharmacology*; 33(3); 574- 587.
2. Crespi F. (2020a). Concurrent tissue oxymetry and blood flowmetry to assess the effect of drugs on cerebral oxygen metabolism. *Biointerface Research in Applied Chemistry* ;10,3; 5552 – 5555.
3. Crespi F. (2020b). Influence of the PPAR gamma receptor Agonist GW7845 on Oxygen Tension andBlood Flow in the Medial-Prefrontal Cortex of Rodents: An In Vivo Flow-Oxymetry Study. *J Clin Neurol Neurosci*; 1:08.
4. Paxinos, G.; Watson, C. (1986). The rat brain in stereotaxiccoordinates. *Plenum Press*; New York; 2nd edn.
5. Ceolin, L.; Schwarz, A.; Reese, T.; Crestan, V.; Bifone. A. (2007). Effects of cocaine on blood flow and oxygen metabolism in the rat brain: implications for phMRI. *Magnetic Resonance Imaging*; 25; 795-800.
6. Crespi, F. (2013). In vivo oxymetric analysis of mild hypercapniaupon cerebral oxygen, temperature and blood flow: markers of mood as proposed by concomitant bupropion challenge andelectrochemical analysis? Exp. *Brain. Res*; 230; 597-604.
7. Rhodes, C. E., Denault, D., & Varacallo, M. A. (2022). Physiology, oxygen transport. In StatPearls [Internet]. StatPearls Publishing.
8. Bremner, J. D., Vythilingam, M., Ng, C. K., Vermetten, E., Nazeer, A., Oren, D. A.,et.al. (2003). Regional brain metabolic correlates of α-methylparatyrosine– induced depressive symptoms: implications for the neural circuitry of depression. *Jama*; 289 (23); 3125-3134.
9. Moylan, S., Maes, M., Wray, N. R., Berk, M. (2013). The neuroprogressive nature of major depressive disorder: pathways to disease evolution and resistance, and therapeutic implications. *Molecular psychiatry*; 18(5); 595-606.
10. Pizzagalli, D. A. (2014). Depression, stress, and anhedonia: toward a synthesis and integrated model. *Annual review of clinical psychology*; 10(1); 393-423.
11. Pizzagalli, D. A., Roberts, A. C. (2022). Prefrontal cortex and depression. *Neuropsychopharmacology*; 47(1); 225-246.
12. Tamburella, A., Micale, V., Leggio, G. M., Drago, F. (2010). The beta3 adrenoceptor agonist, amibegron (SR58611A) counteracts stress-induced behavioral and neurochemical changes. *European Neuropsychopharmacology*; 20(10); 704-713.
13. Schena, G., & Caplan, M. J. (2019). Everything you always wanted to know about β3- AR*(* but were afraid to ask). *Cells*; 8(4); 357.

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